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Review

Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: Consensus from an international survey and discussion program

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ABSTRACT

Navigate PD was an educational program established to supplement existing guidelines and provide recommendations on the management of Parkinson's disease (PD) refractory to oral/transdermal therapies. It involved 103 experts from 13 countries overseen by an International Steering Committee (ISC) of 13 movement disorder specialists. The ISC identified 71 clinical questions important for device-aided management of PD. Fifty-six experts responded to a web-based survey, rating 15 questions as 'critically important;' these were refined to 10 questions by the ISC to be addressed through available evidence and expert opinion. Draft guidance was presented at international/national meetings and revised based on feedback. Key take-home points are:

• Patients requiring levodopa >5 times daily who have severe, troublesome 'off' periods (>1−2 h/day) despite optimal oral/transdermal levodopa or non-levodopa-based therapies should be referred for specialist assessment even if disease duration is <4 years.

• Cognitive decline related to non-motor fluctuations is an indication for device-aided therapies. If cognitive impairment is mild, use deep brain stimulation (DBS) with caution. For patients who have cognitive impairment or dementia, intrajejunal levodopa infusion is considered as both therapeutic and palliative in some countries. Falls are linked to cognitive decline and are likely to become more frequent with device-aided therapies.

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● Insufficient control of motor complications (or drug-resistant tremor in the case of DBS) are indications for device-aided therapies. Levodopa-carbidopa intestinal gel infusions or subcutaneous apomorphine pump may be considered for patients aged >70 years who have mild or moderate cognitive impairment, severe depression or other contraindications to DBS.

1. Introduction

Parkinson's disease (PD) is characterized by motor symptoms, such as bradykinesia, rigidity, tremor and postural instability. In its early stages, treatment with oral dopaminergic therapies is usually effective; however, as the motor disease progresses these therapies no longer provide adequate control of symptoms which range from motor and non-motor fluctuations to dyskinesias. At this stage, it is important to ensure timely referral of patients to a movement disorder specialist before deterioration in quality of life (QoL) and development of complications of advancing disease [1,2]. It may be appropriate to consider device-aided treatments when motor fluctuations become refractory to adjustments in oral/transdermal medication, and when these adjustments are typically complicated by the emergence (or worsening) of dyskinesias [2].

Three device-aided treatments are available:

● subcutaneous (SC) apomorphine pump [3];
● levodopa-carbidopa intestinal gel (LCIG) [4] infusions [5,6];
● deep brain stimulation (DBS) [7].

Alongside motor symptoms, people with PD also experience non-motor symptoms (NMS) such as: pain, drooling; choking/swallowing difficulties; constipation; bladder dysfunction; cognitive impairment; hallucinations; depression/anxiety; sexual dysfunction; insomnia, which occur from disease onset [8]. Non-motor symptoms contribute to severe disability, impaired QoL, and institutionalization [9], and can be more troublesome and disabling for the patient than motor complications [10]. Recent work suggests some NMS are treatable using device-aided therapies [11,12] since they are often dopaminergic in origin. Furthermore, some NMS specifically complicate motor fluctuations, and are treatable by strategies that attenuate fluctuations [13].

Current guidelines provide recommendations based on randomized placebo-controlled studies providing level 1 evidence of treatment. Such evidence is often not available for a range of non-motor issues as well as some motor phenomena. This leads to a lack of pragmatic real-life instruction on how to treat patients with device-aided therapies when oral/transdermal medications no longer effectively control their symptoms [14,15]. Despite multiple evidence-based guidelines, there remain clear gaps in knowledge, which, in clinical practice, are addressed through expert judgment and experience.

To supplement current clinical guidelines, a pan-European educational program, 'Navigate PD', was established to identify the key unresolved issues in the management of PD refractory to oral/transdermal therapies and explore questions commonly raised by clinicians about the optimal use of device-aided treatment. Here we propose approaches for the management of clinically important unresolved issues in PD based on the experience and expert opinion of over 100 experts in the field of PD/neurology.

A total of 103 experts from 13 countries worldwide participated in the Navigate PD program (Working Group members excluding authors of this paper are listed in Acknowledgments). Each country had its own National Steering Committee and the program was overseen by an International Steering Committee (ISC) of 13

specialists from Europe and chaired by two authors of this paper (PO and KRC). The lead authors were contacted and suggested the Steering Committee. AbbVie then contacted a leading MD specialist in each of the participating countries, who could then suggest the specialists participating from each country. The main criteria for participation was to be an internationally recognized movement disorder specialist with well-documented experience with advanced PD therapies.

The objectives of the program were:

● to identify and address the most important questions relating to device-aided management of PD;
● to provide practical answers based on available evidence and the clinical experience of participants; and
● to develop pan-European guidance for PD management beyond oral/transdermal therapy that clearly defines the patient and treatment choices available.

The multi-step program took place between April 2012 and July 2013 and involved numerous international and national meetings attended by neurologists, geriatricians and MD specialists representing many countries. The process is outlined in Fig. 1.

The ISC identified areas of clinical focus and developed 71 key questions (Appendix 1), which were ranked in a web-based survey by the experts. Based on this ranking, the ISC prioritized questions via informal debate, then prepared draft guidance for each based on available evidence from literature reviews combined with expert opinion where evidence gaps existed. The draft guidance was presented and discussed at national and international meetings and revised based on the feedback obtained. This was not a formal consensus or Delphi process; the program aimed to achieve answers on which all participants had reached broad agreement.

Fifty-six completed web-based prioritization questionnaires were returned. Of 71 questions, 15 were rated as 'critically important' by at least one-quarter of respondents. These were further refined by the ISC to 10 questions to be addressed through literature search and expert opinion.

2. Practical guidance on device-aided management of PD derived from discussions of navigate PD

2.1. How do I recognize and refer for specialist assessment a patient in whom the dosage and adjustment of oral/transdermal therapies cannot further improve mobility and quality of life?

Non-invasive therapies may be judged insufficient when QoL becomes inadequate due to motor fluctuations with or without dyskinesias, and the clinician and patient agree that non-invasive therapy alone is no longer effective. Adequate trial of non-invasive therapies includes levodopa and, unless contraindicated, dopamine agonists, monoamine oxidase-B inhibitors and catechol-O-methyltransferase inhibitors. Broadly, referral to a specialist should be considered if levodopa is required ≥5 times daily, although the number of doses is not relevant if tolerated by the patient and an adequate reduction in 'off' time is achieved.

Individuals with >1—2 h of 'off' time during the awake part of the day despite optimized oral/transdermal medical management should be considered candidates for device-based therapies. The severity and quality of a patient's 'off' periods are equally important. Some patients with marked 'off' symptoms should be considered for referral even if their overall 'off' duration appears acceptable. If symptoms continue to be refractory or intolerable side-effects develop, as determined by patient feedback, such as the Patient Diary (Appendix 2), oral/transdermal management is inadequate and further medication adjustment is unlikely to be beneficial.

Motor fluctuations accompanied by troublesome dyskinesias not controlled by addition of amantadine (100—400 mg/day, if available), despite multiple attempts to achieve a patient-acceptable response to non-invasive or transdermal therapies are usually considered an indication for referral for device-aided therapy.

If patients meet the above criteria, referral should be considered, including for patients with a disease duration <4 years.

2.2. What is the relevance of cognitive dysfunction, postural instability and falls in the decision to move to device-aided therapy?

Significant cognitive impairment and postural instability are features of advancing PD characterized by increasing levodopa-resistant symptoms and accelerated motor disability [16]. Risk—benefit analysis of device-aided therapy should consider possible motor improvement and individual risks, as well as expected disease progression with or without device-aided treatment. Cognitive decline, falls and gait problems such as freezing may counteract beneficial responses. However, cognitive issues such as clouding of consciousness, concentration impairment as a manifestation of non-motor fluctuation and freezing may occur during 'off' periods and should be treatable by device-aided therapies [13].

Cognitive assessment should be conducted ideally at 'on' and 'off' stages before initiating device-aided therapy, recognizing that even marked cognitive impairment may be a consequence of a patient's current treatment.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is generally well tolerated in patients with normal age-related cognition. Caution is advised in patients suggestive of imminent or apparent cognitive decline [17]. Patients exhibiting symptomatic cognitive deficits should be excluded because experience has shown a risk of cognitive worsening postoperatively in these patients [18]. DBS of the globus pallidus pars interna (GPi-DBS), which is associated with fewer cognitive risks, may be suitable for patients with mild cognitive impairment [19,20], although this has recently been challenged [21].

Apr 2012
Definition of program goals, process, areas of clinical focus and key clinical questions

May 2012
Prioritization of key clinical questions

June 2012
Literature review for each question

July—August 2012
NSC review of literature repost and consideration of guidance content

July—August 2012
ESC review of literature reports and development of draft guidance statements

September 2012
NAVIGATE PD International Meeting and input into draft guidance statements

September—December 2012
ESC consideration of all feedback and revision of guidance statements

May 2013
ESC review meeting to discuss all guidance statements

July 2013
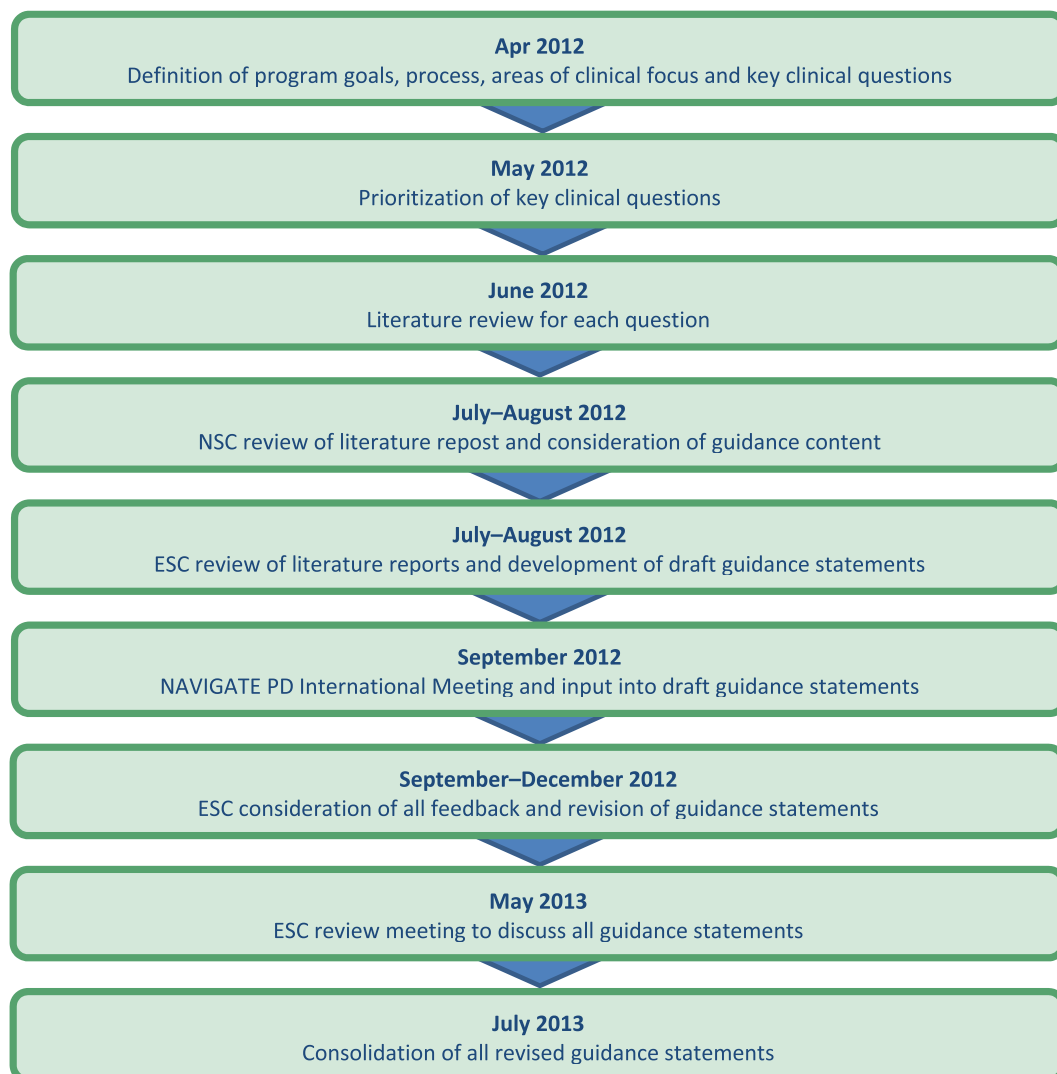Consolidation of all revised guidance statements

Fig. 1. Overview of the process used by the Navigate PD program for developing practical guidance on the device-aided management of Parkinson's disease.

The effects of LCIG infusions or SC apomorphine infusion on cognition are inconclusive [17,22,23]. As with any dopaminergic treatment, an increased risk of confusional states or hallucinations in cognitively impaired patients can be expected, particularly with a potent dopamine agonist treatment, which should be balanced against potential motor benefits. Nevertheless, infusion therapies can be effective in selected patients with cognitive dysfunction. The risk of cognitive decline or neuropsychiatric complications may be greater with SC apomorphine than LCIG infusion. A recent comparative study of apomorphine versus intrajejunal levodopa infusion (IJLI) therapy did not report worsening of hallucinations at 6-month follow-up [24].

LCIG or SC apomorphine infusion can be given in patients with mild cognitive impairment if adequate caregiver support is available. In moderate dementia, LCIG may be considered on an individual basis. In patients with cognitive impairment, the decision to implement device-aided treatment should be made by a movement disorder specialist in consultation with the patient and caregiver, with consideration given to the balance of cognitive impairment and caregiver support.

Device-aided therapy should be considered if a patient's balance/gait responds well to increases in oral levodopa and the patient is stable in the 'off' state. Patients with balance problems due to dyskinesias or levodopa-responsive postural instability may improve with all three device-aided treatments [23,25,26]. Benefits in gait and balance after STN-DBS may be greater and more sustained in younger patients, and are closely linked to the levodopa-responsiveness of axial motor symptoms before surgery [17]. In elderly patients (biological age >70–75 years), STN-DBS does not match the benefits of levodopa on axial symptoms, leading to increased gait or balance problems and more frequent falls after surgery [17,27]. The risk of falling should be considered in older patients. The benefits of DBS of the pedunculopontine nucleus area remain to be clarified.

Subcutaneous apomorphine and LCIG may have positive effects on levodopa-sensitive gait and balance problems or on dyskinesia-related problems [17]. Patients and caregivers should be made aware that gait and balance problems unresponsive to levodopa are less likely to improve on infusion therapy.

2.3. What is the efficacy of each device-aided treatment on motor fluctuations and dyskinesias?

Evidence-based data are limited for device-aided treatments in PD. Randomized controlled trials often exclude patients who reflect real-world populations based on their age and stage of disease. To achieve maximal improvement in 'off' and 'on' time without dyskinesias, physicians may choose any of the three device-related therapies. Although no randomized controlled trials directly compare device-aided therapies, data from separate studies including open-label observational studies show:

1. STN-DBS achieves improvements in motor fluctuations, reducing 'off' time by 25–68%, thus the levodopa equivalent dose can be reduced by 31–68% and dyskinesias reduced by 40–60% [28];
2. SC apomorphine infusion achieves improvements in motor fluctuations and time with dyskinesias by 50–85% and 43–64%, respectively [29–40];
3. LCIG infusions achieve improvements in motor fluctuations and time with dyskinesias of 49–64% and 47–59%, respectively [4,41].

In summary, the effects on 'off' fluctuations are comparable across the device-aided therapies, although for SC apomorphine,

only data from uncontrolled studies are available. All three therapies have an effect on dyskinesias, but these effects are best documented with DBS.

2.4. What is the efficacy of each device-aided treatment on non-motor symptoms?

Non-motor symptoms in advanced PD can be challenging to treat. With the exception of dementia, hallucinations and depression, few clinical studies have been specifically designed to assess other relevant NMS such as apathy, sleep dysfunctions, pain and fatigue. The efficacy of device-related therapies on NMS is supported largely by anecdotal clinical evidence, thus NMS without fluctuations should not be considered as a specific indication for device-aided therapies. However, clinical experience and some clinical data suggest that NMS, particularly those with a dopaminergic basis, respond [42]. Therefore NMS might be considered for helping select the type of device-aided therapy in individual cases. Examples of studies in which device-aided therapies have had beneficial effects on NMS are documented in Table 1.

2.5. What are the adverse events and complications of each device-aided treatment?

The following safety information has come from selected available studies. Study designs, patient populations and methodology for safety monitoring vary so the prevalence of complications and adverse events (AEs) cannot be compared between treatments.

Complications and AEs related to DBS may occur during surgery, in the immediate postoperative period and upon chronic stimulation. The rate and frequency of the most common complications are shown in Table 2. When selecting patients for DBS, clinicians must consider the possible and likely AE profile on a case-by-case basis. The choice of DBS target may depend on individual features, particularly age or mild behavioral changes. The psychiatric status of the patient should be assessed because there may be a risk for developing apathy post DBS. Depression and suicidal risk should be considered in the presence of previous psychiatric history. Balance and dysarthria may worsen and must also be considered. It is important to ensure that the patient is operated on at a center with appropriate surgical expertise and adequate facilities for follow-up and long-term care.

Complications and AEs related to SC apomorphine may occur during the initiation of treatment or ongoing treatment, and can be related to the device or the drug. Limited published data are available on the safety and tolerability of continuous SC apomorphine infusion. In general, available data are derived from case series and case reports [31,33,34,37,38,41,63,64]. The rate and frequency of the most common complications are shown in Table 3. To minimize the risk of complications, patients, caregivers and physicians should ensure optimal care of skin problems, use correct, up-to-date and sterile cannulas, conduct regular blood checks to identify potential autoimmune hemolytic anemia (exceedingly rare) and monitor patients for possible development of dopamine agonist-related behavioral problems.

Complications and AEs related to LCIG infusions may occur during surgical implantation or use of the device, and can be related to the device or the drug. Limited published long-term data are available on the safety and tolerability [49]. The rate and frequency of the most common complications are shown in Table 4. To minimize the risk of complications, an

Table 1
Clinical evidence showing beneficial effects of device-aided therapies on non-motor symptoms (NMS).

- In a small case series, STN-DBS did not have notable immediate effects on NMS, but showed benefit on depression, anxiety and fatigue in some patients over time [43].
- A multicenter European comparative cohort study evaluating the motor and non-motor effects of SC apomorphine infusion and LCIG infusion found that both treatments significantly improved NMS from baseline [44].
- SC apomorphine has been shown to improve NMS in a small comparative study with best oral and transdermal medical therapy, with effects most pronounced on sleep/fatigue, mood/apathy and excessive sweating [45]. Although there are few data, there is a suggestion of some benefit on urinary symptoms.
- LCIG infusion has been shown to significantly improve several non-motor symptom domains, including cardiovascular, sleep/fatigue, gastrointestinal, urinary, and sexual functioning [17,46–48]. It may also have a beneficial effect on depressive symptoms, delusions and impulse control disorders (ICDs) [47,49]. LCIG probably decreases the frequency of spontaneous night-time leg movements, however, data are lacking.
- An open-label, prospective, multicenter, 6 month study comparing 44 patients on LCIG infusion and 43 patients on apomorphine infusion, sleep/fatigue, gastrointestinal, urinary and sexual dimensions of the NMS scale showed significantly higher improvement with LCIG infusion compared with apomorphine infusion. Furthermore, LCIG improved QoL and NMS in 75% of patients; apomorphine infusion improves QoL and NMS in 75% and 40% of patients, respectively [24].
- 'Off'-related pain has been shown to respond to STN-DBS in a 2-year follow up study [50]. It responds also to GPi-DBS, which has been demonstrated at 1-year follow-up [51]. There is evidence from uncontrolled studies showing an improvement in pain with LCIG infusion and with apomorphine infusion.
- Small case series have suggested that objective and subjective sleep symptoms may improve following DBS [17,52–55], LCIG infusion [46,47,56], and apomorphine infusion [45].
- In patients with severe impulse control disorders, DBS may be a useable treatment option [57]. However, there are conflicting data on the effect of DBS in patients with impulse control disorders or dopaminergic dysregulation syndrome, with aggravation in some and marked improvements in others, if dopaminergic medication withdrawal was tolerated [17]. LCIG infusion may also be effective as it allows tapering or withdrawal of oral dopamine agonists [58].
- An observational, 2-year follow-up study of 19 patients receiving LCIG infusion found that LCIG infusion confers a low risk of developing impulse control disorders and may be useful in the management of refractory impulse control disorder (*A Todorova*; abstract presented at MDS' ICDs in PD conference, Oct 2012).
- In a survey in which 41 patients receiving SC apomorphine were screened for development or attenuation of impulse control disorder, SC apomorphine was associated with a 9.7% risk of development of impulse control disorder (*A Todorova*; *abstract presented at MDPD, Apr 2013*).

Table 2
The rate and frequency of the most common adverse events and complications associated with deep brain stimulation.

	Relatively frequent (≥10%)	Infrequent (<10% to ≥5%)	Rare (<5%)
Surgical complications			
Death (within 30 days postoperatively)			0–2.6%
Symptomatic intracerebral hematoma			0–1.3%
Asymptomatic intracerebral hematoma			0–2.6%
Postoperative confusion (mild to moderate)		2.7–5.1%	
Pulmonary embolism			0–1.1%
Urinary retention			0–2.2%
Device-related complications			
Infection at hardware site		2.6–9%	
Extension cable discomfort			0–2.6%
Subcutaneous seroma		0–5.1%	
Skin erosion		0–5.1%	
Hardware dislocation/fracture			0–3.2%
Technical device failure			0–2.4%
Other post-surgical AEs (related to stimulation or to PD)			
Anxiety			0–4.8%
Apathy			0–4.8%
Balance and gait problems	8.2–13.7%		
Cognitive disturbances		0.8–5.1%	
Daytime sleepiness			0–4.0%
Depression	4.8–16.9%		
Dysarthria	5.8–10.3%		
Dyskinesias increased	0.8–25.6%		
Dystonia		0–6.6%	
Falls		1.6–7.1%	
Fluctuations		0–8.8%	
Fractures from falls			0–1.3%
Freezing/worsening of mobility	5.8–32%		
Pain	0–15.3%		
Psychosis		0–5.1%	
Seizures			0–1.1%
Suicide attempt			0–1.6%
Suicide committed (chronic stimulation)			0–1.3%
Weight change	0–12%		

*Based on four large (>50 patients) randomized controlled trials comparing DBS with best medical management in Parkinson's disease [59–62]. Note that patients collectives differ in the studies evaluated (grade of advancement of PD), follow-up times differ, and it is not possible to differentiate in many reports whether side effects were transient or permanent, nor whether they were mild, moderate or severe.
AE, adverse event; PD, Parkinson's disease.

experienced gastroenterologist who is familiar with the infusion system used should be involved. Close collaboration between the neurologist and gastroenterologist is essential. Patients should be monitored for peripheral neuropathy, weight loss and vitamin B$_{12}$ status.

2.6. Which patient should not be considered for each or any device-aided therapy?

Relative and absolute contraindications to device-aided therapies are shown in Table 5. Lack of a response to levodopa

Table 3
The rate and frequency of the most common adverse events and complications associated with subcutaneous apomorphine.

	Relatively frequent (≥10%)	Infrequent (<10% to ≥5%)	Rare (<5%)
Administration/device-related complications			
Needle/injection-site pain	35.0% [35]		
Apomorphine-related complications			
Nodules	41−100.0% [23,32,36,65]		
Weight gain	60.0% [35]		
Neuropsychiatric AEs	36.4−44.0% [32,36]		
Daytime somnolence	31.0% [35]		
Nausea	4.0−18.2% [32,36]		
Orthostatic hypertension	16.0% [36]		
Mild sedation	13.6% [32]		
Coombs antiglobulin positive	12.5% [35]		
Hemolytic anemia		0.6−9.1% [35,23,32]	
Urinary urgency		8.0% [36]	
Abscess			1.6−4.0% [35,36]
Necrosis			0−4.0% [36,65]
Hyperlibidinous effect			4.0% [36]
Diarrhea			4.0% [36]

AE, adverse event.

(with the exception of rest tremor for DBS) is an absolute contra-indication for all device-aided therapies and non-compliance with non-invasive therapies is considered to be a risk factor, although not an absolute contraindication.

2.7. What information about each device-aided therapy should be conveyed to a patient and caregiver?

Patients and caregivers must be committed to the device-aided treatment and aware that it is not disease-modifying and that the patient must endure an operation (for DBS and LCIG infusion) and numerous follow-up visits.

The clinician must manage the expectations of the patient and caregiver in terms of QoL and ability to perform activities of daily living, ensuring an understanding of realistic treatment goals in terms of short- and long-term outcomes. Patients and caregivers should understand that improvements will be an increase in 'on' time duration (decrease in 'off' time), but the level of symptom improvement will not be greater than that achieved when at their most responsive to oral therapies, except possibly for reduced dyskinesia (and with the exception of tremor in the case of DBS). Some symptoms may not improve with device-aided therapy (mainly NMS, but also motor symptoms, such as instability, falls or freezing when present during 'on').

Each device-aided therapy can be associated with side-effects and complications, and device malfunction/failure. Patients should be advised on how to manage the device after discharge, troubleshoot potential problems and prepare medication in order to make an informed decision on whether they or their caregiver can manage the treatment. In many countries, validated patient-related outcome tools are likely to be recommended for routine use in advanced therapies [67].

The information given to the patient and caregiver should be patient-specific, i.e. physicians should only discuss in detail potential treatment options available for that patient. However, patients should have access to all information so they feel fully informed. Patients and caregivers can be directed to reliable web-sites, such as those provided by PD patient associations. Further guidance on providing information to patients/caregivers is given in Appendix III.

2.8. When is the right time to inform a patient about device-aided treatment options and how should they be informed about the treatments? What tools and consultation techniques should be used when communicating information to patients?

Device-aided therapy options should be discussed before patients become candidates for the devices so they can be reassured that there are treatment options for the future. Patients at high risk for developing motor complications, particularly young-onset patients, should be informed early on about the availability of device-aided therapies.

If possible, balanced information should be given by a physician with personal experience of all three device-aided therapies and aware of the possibility of bias based on their own experience and preference. Information on all device-aided therapies should be provided, including brief information on any not indicated or rec-ommended for an individual patient to reassure them that they have received all available information. The physician should also give an opinion on the most appropriate treatment for an individual patient.

Discussing device-aided treatments is a stepwise process, which may occur over several years:

- first, the idea should be introduced;
- at later visits, greater detail should be provided;
- finally, full information should be given and the patient's consent obtained.

Communication tools should be standardized and unbiased e.g. literature from patient associations and medical professional soci-eties, but the information also needs to be individualized, e.g. based upon a patient's age or caregiver's ability. A patient may need to be told why a certain treatment is inappropriate for him/her, e.g. DBS in the elderly patient.

Depending on a patient's level of interest, the use of videos or directing them to websites may be appropriate. Talking to a specialist nurse or other health professional who deals with the practical aspects is helpful and recommended, as may be direct demonstration of the device(s) under consideration. In the case of pump treatments, involving district nurses or other professional caregivers to help with setting up the pump, e.g. each morning, should be explored and discussed when appropriate. For some

Table 4
The rate and frequency of the most common serious adverse events, adverse events and complications associated with levodopa-carbidopa intestinal gel infusion.

	Relatively frequent (≥10%)	Infrequent (<10% to ≥5%)	Rare (<5%)
Surgical/device-related complications			
Complication of device insertion	21.4–56.6% [4,41,66]	6.8% [41]	
Procedural pain	17.7–29.7% [4,41,66]		*0.8% [66]*
Post-operative wound infection	10.4–21.0[a]% [4,41,66]		
Incision site erythema	9.4–18.9% [4,41,66]		
Medical device site reaction	38.0[a]% [66]		
Device dislocation	34.7[a]% [66]		*1.6% [41]*
Device occlusion	29.4[a]% [66]		
Device-related infection	21.3[a]% [66]		
Device connection issue	21.3[a]% [66]		
Device breakage	11.9[a]% [66]		
Unintentional removal of device by patient	10.6[a]% [66]		
Device leakage		8.9[a]% [66]	
Procedural site reaction		8.9[a]% [41]	
Post procedural discharge	8.3–10.9[a]% [4,41,66]		
Incision site pain		5.3[a]% [66]	
Other			
Abdominal pain	30.7–34.2[a]% [41,66]		*1.5[a]–4.7% [41,66]*
Flatulence	16.2% [4]		
Constipation	13.5–21.6% [4,41]		
Nausea	13.5–29.7% [4,41]		
Excessive granulation tissue	13.5–18.2% [41,66]		
Fall	10.9% [41]		
Dyskinesia	10.9% [41]		
Insomnia	10.8–10.9% [4,41]		
Anxiety	10.4% [41]		*1.0% [41]*
Headache		8.9% [41]	
Diarrhea		8.3% [41]	
Oropharnygeal pain		8.3% [41]	
Weight decreased		8.3% [41]	
Orthostatic hypotension		8.3% [41]	
Dyspepsia		7.8% [41]	
Urinary tract infection		7.8% [41]	
Depression		7.3% [41]	*1.6% [41]*
Vomiting		7.3% [41]	
Pneumoperitoneum	7.3–10.8% [4,41]		*0.5[a]–3.6% [41,66]*
Back pain		6.8% [41]	*1.0% [41]*
Pain in extremity		5.7% [41]	
Sleep attacks		5.7% [41]	
Confusional state		5.4% [4]	
Pertitonitis			*1.8[a]–3.1% [41,66]*
Polyneuropathy			*2.1% [41]*
Hip fracture			*1.6% [41]*
Pneumonia			*1.6–1.8[a]% [41,66]*
Syncope			*1.6% [41]*
Radius fracture			*1.0% [41]*
Pyelonephritis			*1.0% [41]*
Small intestinal obstruction			*1.0% [41]*
Acute abdomen			*0.5[a]% [66]*
Gastrointestinal hemorrhage			*0.5[a]% [66]*
Paralytic ileus			*0.5[a]% [66]*
Intestinal ischemia			*0.5[a]% [66]*
Intestinal perforation			*0.5[a]% [66]*
Sepsis			*0.5[a]% [66]*

Serious adverse events are in *italics*.
[a] In patients who received a percutaneous endoscopic gastrostomy jejunal extension tube.

patients, an opportunity to interact directly with other patients already on a device-aided treatment, e.g. at patient support groups, may be particularly helpful. The physician should encourage involvement in PD patient associations to help patients become better informed.

2.9. How do I manage non-invasive therapy in a patient on device-aided treatment?

During the first phase of treatment (≤3 months after initiation), the movement disorder specialist is responsible for adjustments to both the device-aided treatment and non-invasive therapies, ensuring that the referring neurologist is fully informed of all

treatment decisions. Access to patient records is essential to understand previous treatments and doses and the parameters for which the device-aided therapy has been introduced.

Anti-PD treatment should be restarted after DBS to relieve discomfort and limit the risk of acute dopaminergic withdrawal and neuroleptic malignant syndrome. The aim is to balance stimulation effects and concomitant medication. Dopaminergic medication is decreased to reduce the risk of dyskinesia, sedation, excessive daytime sleepiness and confusion. Aggressive medication reductions should be avoided because they may lead to the re-emergence of motor and NMS.

Subcutaneous apomorphine can be considered as monotherapy or as an add-on to levodopa depending on the patient's tolerance of

Table 5
Relative and absolute contraindications to device-aided therapies for the management of Parkinson's disease.[a]

Device-aided therapy	Increasing risk	Absolute contraindications
DBS	• Non-compliance with non-invasive therapies • Biological age >70—75 years[b] • Severe depression • Condition that increases surgical risk, including cardiomyopathy	• Lack of levodopa response, with the exception of rest tremor • Dementia • Severe brain atrophy or lesions interfering with trajectory planning
SC apomorphine	• Non-compliance with non-invasive therapies • MCI or dementia • Previous or current dopamine dysregulation, punding or impulse control disorders • Moderate-to-severe dementia	• Lack of levodopa response • Inability of patient and caregiver to handle medication and device
LCIG infusion	• Non-compliance with non-invasive therapies • Pre-existing peripheral neuropathies[c] • Previous or current dopamine dysregulation and punding • Moderate-to-severe dementia • Patient frailty (unable to support device weight)	• Lack of levodopa response • Inability of patient and caregiver to handle medication and device • Absolute or relative contraindications to abdominal surgery

DBS, deep brain stimulation; LCIG, levodopa-carbidopa intestinal gel; MCI, mild cognitive impairment; SC, subcutaneous.
  [a] For a complete list of device-related absolute contraindications, the clinician is referred to the manufacturers' product information.
  [b] Clinicians should take into account the frailty of a patient, along with other comorbidities.
  [c] Clinician should investigate the reason for neuropathy to determine whether it is clinically relevant/symptomatic.

infusion rate. Patients should usually be premedicated with domperidone to suppress nausea and vomiting. In view of the risk of prolonged QT interval associated with domperidone, the European Medicines Agency recently restricted the recommended dose to a maximum of 10 mg tid. Domperidone can often be discontinued over subsequent days/weeks. An alternative to domperidone is oral trimethobenzamide (300 mg tid) started 3 days before the initial dose of SC apomorphine and continued at least during the first weeks of therapy. During the initiation phase, the specialist center will usually discontinue oral dopamine agonists and gradually reduce or discontinue the levodopa dose in patients with dyskinesias (with the exception of early morning and late night) in a stepwise manner over several days to weeks. On discharge, any further reductions in the patient's oral medication are either explicitly recommended to the referring physician or are performed at the center. If a patient is on a 12—14-h infusion, night-time therapy may be required to avoid severe rebound phenomena during the night and early morning; rotigotine transdermal patch used overnight has been shown to be useful in this regard [68].

LCIG infusion can be given as monotherapy at the physician's discretion. The transfer from regular therapy to LCIG can be abrupt (overnight) or slow over days/weeks based on the patient's condition and response. Long-acting L-dopa or dopamine agonist perorally/transdermally may be given in the evening to cover the night if necessary. In some patients, combination with a dopamine agonist might be beneficial. Amantadine can be given additionally for remaining troublesome dyskinesias [69]. The possible association of LCIG infusion with an increased risk of polyneuropathy is under investigation. Assessment of vitamin B12 levels before and during treatment is recommended. Many centers provide vitamin B12 substitution to all patients, although the precise indication for vitamin B12 substitution has not been clarified [70].

Management of PD patients in the longer term phase of device-aided therapy may be overseen by the referring neurologist. Education should be provided to neurologists to enable this responsibility. Medications can be titrated within defined parameters to address worsening or new motor deficits. For patients presenting with sudden worsening of function, the functionality of the device should be considered. The specialist team should be consulted regarding adjustments to device-aided therapies and patients should be referred to the specialist team every 6 months for review. For patients receiving LCIG infusion therapy, referral may be as frequent as every 3 months, up to 6 months after surgery, and once- or twice-yearly thereafter.

2.10. What factors would indicate the selection of one device-aided treatment over another?

Insufficient control of motor complications (or drug-resistant tremor [only in the case of DBS]) is the most common reason for moving from non-invasive to device-aided therapies [71,72]; potential control of some NMS may also be considered. Adverse events and complications of non-invasive therapies can contribute to the decision to switch to a device-related therapy. The goal of treatment should be 24-h symptom control. Table 6 illustrates how specific PD-related and treatment-related symptoms may influence the decision to use one device-aided therapy over another.

Treatment decisions should take into account symptoms, response to optimal oral therapy, comorbidities, age, caregiver support, and patient/caregiver preference:

- For patients aged <70 years with motor fluctuations or dyskinesias who are otherwise healthy, any of the device-aided therapies may be considered.
- For patients aged >70 years, DBS surgery should be considered second-line among the device-aided therapies (although patients can be operated on in the presence of a normal MRI and preserved cognitive function).
- For patients aged >70 years with mildly or moderately impaired cognition (or other contraindications to DBS), LCIG infusions or SC apomorphine may be considered with cessation or reduction in oral therapy (note that rapid cessation of dopamine agonists may lead to withdrawal symptoms).

3. Conclusions

The Navigate PD program was not intended to provide formal guidance on the management of Parkinson's disease refractory to oral/transdermal medication and cannot supplant existing national and international guidelines. Rather, the guidance offered complements existing guidelines, particularly for some areas of device-aided management of PD not covered by existing resources or where published evidence is lacking.

Limitations of the program include the acceptance of non-level 1 studies in the absence of comparative studies of advanced therapies and consolidation of the feedback on the draft guidance to formulate the final guidance mainly through informal discussion rather than formal consensus. The program design allowed incorporation of individual clinical experience into development of answers, thus not always based on high-level evidence. However,

Table 6
The influence of specific Parkinson's disease- and treatment-related symptoms on the decision to use one device-aided therapy over another.

Symptom	SC apomorphine pump	LCIG	STN-DBS
Dyskinesias	+	+	++
Slight ongoing hallucinations	+/−	+/−	+/−
Drug-related hallucinations and/or delusions in patient history	+/−	+	+
Marked ongoing hallucinations/psychosis (delirium)	−	+/−	−
Impulse control disorders	−	+	+
Drug-related daytime somnolence	−	+/−	+/−
Maintenance insomnia	+	+	+
Mild cognitive impairment	+/−	+	+/−
Dementia	−	+/−	−
Pronounced therapy-refractory depression	+	+	−
Non-motor fluctuations[a], (e.g.: anxiety, pain, clouded thinking, apathy)	+	+	+
Dysphagia	+/−	+/−	−
Dysarthria	+	+	−
L-dopa-unresponsive postural and gait problems, falls	+/−	+/−	−
Restless legs	+	+	+/−
Orthostatic hypotension	−	+/−	+/−

++, presence of side effect/complication strongly strengthens the decision to select the device-aided therapy.
+, presence of side effect/complication strengthens the decision to select the device-aided therapy.
+/−, presence of side effect/complication needs further investigation.
−, presence of side effect/complication speaks against selecting the device-aided therapy.
LCIG, levodopa-carbidopa intestinal gel; SC, subcutaneous; STN-DBS, subthalamic nucleus deep brain stimulation.
This information is based largely upon clinical experience and expert opinion in the absence of robust published evidence from comparative studies and does not suggest a particular treatment is warranted due to the presence of a particular symptom or AE, rather it suggests that a particular treatment is acceptable in a given situation and, thus, may contribute to any informed decision.
  [a] If non-motor fluctuations are present, all the device-aided treatments may be considered.

feedback was obtained from >100 experts across multiple specialist centers, which could be regarded as a strength.

Contributors

All authors were members of the Steering Committee; participated in local and international meetings and discussions on Navigate PD; conducted research and article preparation, participated in the elaboration of first draft and reviews of the manuscript. All authors reviewed and approved the final version of the manuscript.

Disclosure and role of funding source

Conflicts of interest

PO has given lectures with honoraria and/or had expert advisor role for the following companies: Abbott/AbbVie, Britannia, Bayer, Evidera, Orion Pharma, UCB.

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JTS has received compensation from AbbVie for scientific advisory boards; compensations from Teva and UCB Pharma for speaking services and research support from AbbVie and Biotie.

JV reports grants and personal fees from Medtronic, personal fees from St. Jude, grants and personal fees from Boston Scientific, personal fees from UCB, personal fees from Merz, personal fees from Allergan, personal fees from TEVA, personal fees from Novartis, personal fees from AbbVie, outside the submitted work.

ED has participated in advisory boards for Britannia and Global Kinetics Corporation, and has received speaker's fees from AbbVie, GlaxoSmithKline, Medtronic, Nordic Infucare and Zambon.

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JKK is a consultant for Medtronic and Boston Scientific and has received fees for speaking from St Jude.

TH has received speaker's fees from AbbVie Denmark, and has participated in advisory boards for Britannia.

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Appendix A. Supplementary data

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